REMARKS

Upon entry of the amendment, claims 27-29 and 32 are pending in this application. Claims 1-26 were previously cancelled and claims 30, 31 and 33-38 are cancelled in this paper, without prejudice to or disclaimer of the subject matter contained therein. Claims 27, 28 and 32 are amended.

The amendments are solely for advancing prosecution. Applicants, by amending or cancelling any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert the original claim scope of any claim amended herein, in a continuing application.

Claim 27 has been amended to recite "a method for enhancing the efficiency of transduction of a nucleotide sequence of interest into a target cell, comprising: (a) providing a recombinant adenovirus comprising a relaxin-encoding nucleotide sequence which is operatively linked to a regulatory sequence directing its expression, and a nucleotide sequence of interest to be delivered into the target cell; and (b) contacting the recombinant adenovirus with the target cell for the recombinant adenovirus to infect the target cell, wherein the relaxin protein expressed from the infected target cell enhances the efficiency of transduction of the recombinant adenovirus into the target cell." Claims 28 and 32 have been amended accordingly. Support for the amended claims can be found throughout the specification and claims as originally filed.

No new matter has been introduced to this application within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendment is respectfully requested.

In view of the following, further and favorable consideration is respectfully

requested.

I. Rejections of Claims 27-31 and 33-35 under U.S.C. §102(b) and §102(e)

The Examiner has rejected claims 27-31 and 33-35 under 35 USC §102(b) and §102(e) as being anticipated by *Hirsch et al.* (U.S. Publication No. 2003/0003583). As the basis for the rejection, the Examiner asserts that *Hirsch et al.* discloses a method of delivering a gene into cells for the treatment of cancer (0151), the method comprising the use of an adenoviral gene delivery system (0019) wherein the gene may encode relaxin (0140). The Examiner also asserts that the "enhancing transduction efficiency" as recited in the claims is considered a functional property inherent to the relaxin protein expressed by the gene delivery system of *Hirsch et al.*, absent evidence to the contrary.

Applicants respectfully traverse these rejections. The test for anticipation under 35 USC §102 is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). Moreover, the rule of law requires that the Examiner must consider a reference in its entirety in determining the scope and content of the reference. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, (Fed. Cir 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, the Examiner must acknowledge any disclosure in the reference that teaches away from the present invention. *Id.*

Further, subject matter is only inherent when extrinsic evidence makes it clear that the subject matter is necessarily present in (i.e., necessarily flows from) the disclosure of cited art. Ordinarily skilled artisans however need not recognize this presence at the time of invention. MPEP §2112. Inherency cannot be established by mere possibilities or even probabilities. The fact that a certain result or characteristic may occur or may be present in cited art is not sufficient to establish the inherency of that result or characteristic. MPEP §2112 (IV), citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) reversing a rejection based on inherency because result due to optimization of conditions was not necessarily present in the prior art.

Further, the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957); MPEP 2112.02.

Applicants from the outset point out that claims 30, 31 and 33-38 have been cancelled rendering the rejections *moot* with respect to these claims. Applicants submit regarding the other claims that *Hirsch et al.* fails to teach each and every element of the present claims as arranged as required by the claims, as follows.

Currently pending claim 27 is directed to a method for ***enhancing the efficiency transduction*** of a nucleotide sequence of interest into a target cell, comprising: (a) providing a ***recombinant adenovirus*** comprising a ***relaxin-encoding nucleotide sequence*** which is operatively linked to a regulatory sequence directing its expression, and ***a nucleotide sequence of interest to be delivered into the target cell***; and (b) contacting the recombinant adenovirus with

the target cell for the recombinant adenovirus to infect the target cell, wherein the relaxin protein expressed from the infected target cell enhances the efficiency of transduction of the recombinant adenovirus into the target cell. Claims 28 and 32 are dependent from claim 27, and require all of the elements of claim 27.

Hirsch et al. ***does not teach the "recombinant adenovirus"*** as claimed, which comprises a ***"relaxin-encoding nucleotide sequence"*** and a ***"nucleotide sequence of interest to be delivered into the target cell"*** at the same time. *Hirsch et al.* describes a recombinant adenovirus, but it is only as a ***helper*** virus containing ***no target genes***. See paragraphs [0028] and [0071]. As a delivery vector, *Hirsch et al.* teaches only an adeno-associated virus (AAV) that may, as a target gene, contain relaxin. That is, in the *Hirsch et al.* method which involves providing cells containing and capable of expressing at least one DNA construct encoding a target gene, a therapeutic gene is delivered in vivo by the AAV to a tissue that is not normally transduced by the AAV, and the tissue that is not normally transduced by the AAV is one that shows low level expression of a transgene without the addition of a proteosome inhibitor or an AAV helper construct or helper virus, such as the adenovirus.

Accordingly, *Hirsch et al.* fails to teach a recombinant adenovirus comprising a relaxin-encoding nucleotide sequence and a nucleotide sequence of interest to be delivered into a target cell together, as required by the present claims.

Further, *Hirsch et al.* discloses relaxin as one of hundreds of potential target genes that can be contained in the AAV, with no specific description or working examples thereof. The expression of relaxin gene, assuming *arguendo* that it is contained in the AAV disclosed in *Hirsch et al.*, is regulated by the administration of

a proteasome inhibitor or a helper virus. The key feature of the AAV as disclosed in *Hirsch et al.* is that the induction of a therapeutic gene expression in the recombinant AAV is conducted by the administration of a proteasome inhibitor or with the help of adenovirus containing no target genes. The method of *Hirsch et al.* to deliver a selected gene to a cell and its expression, therefore, can be successfully accomplished only when the cell or tissue is contacted with a proteasome inhibitor or a helper virus, such as the adenovirus particles.

In this regard, the Examiner asserts that Figures 1 and 3-4 of *Hirsch et al.* clearly demonstrate that the transgene expression occurs in the absence of proteosome inhibitors and thus the recombinant AAV of *Hirsch et al.* encoding a relaxin transgene possesses the property of enhancing the transduction efficiency of the recombinant virus. *See* page 6 of Official Action.

However, Applicants note that, as clearly described in paragraphs [0027] and [0154], Figure 1 teaches that the enhanced expression of a mouse IL-10 transgene by the inclusion of a proteosome inhibitor zLLL, was transient and the expression was "lost" at day 7. Figure 3 teaches that the *in vivo* transduction of RA synovium by rAAV is "enhanced by the addition of adenovirus particles," *see* paragraph [0029], and Figure 4 teaches that the zLLL-induced enhancement of transgene product may be mediated by upregulation of gene transcription or mRNA stability. Considering the disclosure of *Hirsch et al.* when taken in its entirety, that a therapeutic gene is delivered *in vivo* by the AAV to a tissue that is not normally transduced by the AAV, and the tissue that is not normally transduced by the AAV is one that shows low level expression of a transgene without the addition of an AAV helper construct or helper viruses, Figures 1, 3 and 4 do consistently teach that the AAV of *Hirsch et al.*,

whether or not a target gene is included therein, shows a low level expression of the transgene in the tissue without the addition of a proteosome inhibitor or a helper construct. These figures of *Hirsch et al.* do not teach that the AAV, when containing relaxin, has a property of enhancing the transduction efficiency of a nucleotide sequence of interest into the target cell.

Applicants further submit that *Hirsch et al.* does not, expressly or inherently, teach enhancing the transduction efficiency of a nucleotide sequence of interest into a target cell by the recombinant adenovirus as recited in the claims. *Hirsch et al.*, as described in the abstract and throughout the entire reference, teaches ***regulating gene expression*** by a proteasome inhibitor or a helper construct. In other words, the method for enhancing the efficiency of transduction of a nucleotide sequence of interest into the target cell using a recombinant adenovirus containing a relaxin-encoding nucleotide and the nucleotide sequence of interest, as recited in claim 27, is not, inherently or expressly, anticipated by *Hirsch et al.*

In this regard, Applicants note that MPEP 2112.02 provides that new and unobvious uses of old structures and compositions may be patentable; a new and unobvious use of old structure or composition can be acknowledged if the use is unexpected. *See* also *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978).

As demonstrated by the Examples and Figures as presented in the originally filed specification and drawings (also the previously submitted color drawings), the relaxin protein expressed in the cell infected with the recombinant adenovirus having genes of relaxin and Lac Z remarkably enhanced the efficiency of transduction (i.e. infection) of the other recombinant adenovirus into the target cell. This property of

the relaxin-containing recombinant adenovirus is not inherently present in the recombinant AAV of *Hirsch et al.* It is clear that the property of the relaxin to enhance the transduction efficiency of the polynucleotide to be delivered into a cell is ***unexpected*** from *Hirsch et al.* The "enhancing the efficiency of transduction of a nucleotide sequence of interest into a target cell" as recited in the preamble of the present claims is not a description of a merely intended use of a relaxin, as the Examiner alleges in the Official Action, but rather is a description of a ***distinct feature*** of the claimed method over the prior art.

Applicants submit that one of the major barriers to success of gene therapy is a low transduction efficiency of a gene into the target cell. Many attempts have been made to develop a gene delivery system having a ***high efficiency of the transduction of the gene***. For instance, Reference 1 [*Cancer Gene Therapy* (2003) 10, 421-431, Naoki Okada] describes that the authors demonstrated that a RGD fiber-mutant adenovirus (AdRGD) exhibited markedly superior gene transduction efficiency in mouse bone marrow-derived DCs (mBM-DCs) compared to conventional adenovirus vector (Ad) (*See* Abstract and the entire article). Reference 2 [*Cancer Gene Therapy* (2003) 10, 1528-1534, C Wang] also describes that the authors verified that rAAV1 vector (rAAV1-GFP) has a 13-35-fold greater transduction efficiency than that of the rAAV2 vector (rAAV2-GFP). (*See* Abstract and entire article). Reference 3 [*Human Gene Ther* (2001) Mar 1; 12(4):391-9] describes the result of testing whether the expression level of primary and secondary adenovirus receptors, that is, CAR and integrins, are predictive of the efficacy of adenoviral gene transfer in ovarian cancer cells. This article shows that integrin alpha(v)beta(3) plus minimum level of CAR is critical for the adenoviral transduction

efficiency (ATE). Reference 4 [*Current Molecular Pharmacology*, 2008, 1, 13-23] describes that vectors and their administration methods can be extensively modified to decrease the injected dose and increase the transduction efficiency, and it introduces certain developed techniques to increase transduction efficiency. (*See* "VECTOR ADMINISTRATION," on pages 1 and 2). All of the four references are listed in an Information Disclosure Statement submitted herewith.

As seen from the references, the feature of "enhancing the efficiency of transduction of a nucleotide sequence of interest into a target cell" as recited in the present claims should be acknowledged as a distinct feature of the claimed method.

For at least the reasons discussed above, Applicants submit that *Hirsch et al.* fails to teach each and every element of the present claims as arranged in the present claims, as required by *Verdegaal Bros. v. Union Oil Co. of California* and *In re Bond,* respectively. Particularly, *Hirsch et al.* fails to teach a recombinant adenovirus comprising a relaxin-encoding nucleotide sequence and a nucleotide sequence of interest to be delivered into the target cell, as required by the present claims. Accordingly, *Hirsch et al.* does not anticipate the present claims under 35 USC §102(b) or under 35 USC §102(e).

Therefore, Applicants respectfully request the Examiner to reconsider and withdraw these rejections.

II. Rejections of Claims 32 and 36-38 under U.S.C. §103(a)

The Examiner has rejected claims 32 and 36-38 are rejected under 35 U.S.C. §103(a) as being unpatentable over *Hirsch et al.* in view of *Hallenbeck et al.* (U.S. Patent No. 5,998,205) and *Dalemans et al.* (U.S. Patent No. 6,136,594).

The Examiner asserts that it would have been obvious to a skilled artisan to

substitute a first adenovirus expression vector as taught by *Hirsch et al.* with a second adenovirus expression vector comprising a deletion of the E3 region into which the relaxin-encoding nucleotide is inserted, inactivation of the E1B 19 and/or E1B 55 genes, and/or an active E1A gene as taught by *Hallenbeck et al.* and *Dalemans et al.* with a reasonable expectation of success, because such substitution of one known element for another would have yielded predictable results to the skilled artisan at the time of the invention.

Claims 36-38 have been cancelled making the rejection thereof *moot* with respect to these claims. Claim 32 is dependent from claim 27 and includes all the elements of claim 27. Applicants respectfully traverse the rejection of claim 32, for the reasons stated above in Section I for independent claim 27 from which claim 32 is dependent.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc., 550 U.S. 398 (2007)*, a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc.* v. *Chugai Pharm. Co.*, 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

The discussion on the teachings of *Hirsch et al.,* made above in Section I, is incorporated herein in its entirety. Accordingly, ***Hirsch et al. fails to teach a***

recombinant adenovirus comprising the relaxin-encoding nucleotide sequence and the nucleotide sequence of interest to be delivered into the target cell, as required by the present claims.

Neither Hallenbeck et al. nor Dalemans et al. remedies the deficiencies of Hirsch et al. *Hallenbeck et al.* describes a targeted gene therapy using recombinant vectors, particularly replication-conditional vectors and methods for using them. *Hallenbeck et al.* has been cited by the Examiner since the reference describes recombinant adenoviral expression vectors comprising a deleted E3 region in which the gene of interest to be expressed is inserted, said vector comprising an active E1 A gene operatively linked to a heterologus, tissue-specific transcriptional regulatory sequence. *Dalemans et al.* describes a replication deficient recombinant adenovirus vector in the genome of which is inserted an expression cassette comprising the DNA fragment coding for the human CFTR protein, said DNA fragment being placed under the control of the elements for the expression thereof. This reference has been cited by the Examiner since it describes replication deficient adenovirus vectors in which the majority of E1B genes and E3 region are inactive.

However, neither *Hallenbeck et al.* nor *Dalemans et al.* teaches or suggests a recombinant adenovirus comprising a relaxin-encoding nucleotide sequence and a nucleotide sequence of interest to be delivered into the target cell, as required by the present claims. Accordingly, *Hallenbeck et al.* and *Dalemans et al.* cannot remedy the deficiencies of *Hirsch et al.*

Applicants submit that *Hirsch et al., Hallenbeck et al.* and *Dalemans et al.,* taken alone or in combination, fail to teach or suggest all of the limitations of the

present claims, as required by *In re Wilson*, and therefore cannot render the presently pending claims obvious within the meaning of 35 USC §103(a). Reconsideration and withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants submit that the pending claims are in condition for allowance. Early notice to this effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

/Joshua B. Goldberg/

Date: February 2, 2012

THE NATH LAW GROUP
112 S. West Street
Alexandria, Virginia 22314
Tel: (703) 548-6284
Fax: (703) 683-8396

Joshua B. Goldberg
Reg. No. 44,126
Mih Suhn Koh
Reg. No. 65,080
Customer No. 20529